FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

Endocrinologic and Metabolic Drugs Advisory Committee
Hilton Hotel, Washington DC/Silver Spring, Maryland
July 19, 2011

Draft Questions to the Committee

Efficacy

1. Dapagliflozin's efficacy is dependent on the amount of glucose filtered through the glomeruli. As the glomerular filtration rate (GFR) declines in renal impairment, the efficacy of the SGLT-2 inhibitor is also diminished. Please discuss the implications of this reduced efficacy in T2DM where renal impairment can impact a sizeable proportion of patients with this disease. Please include in your discussion whether additional studies (e.g., in special populations) should be conducted to better characterize the efficacy of dapagliflozin in T2DM or whether monitoring for renal function should be performed prior to and/or during treatment with dapagliflozin.

Hepatic Safety

2. Five patients treated with dapagliflozin developed ALT or AST > 3x ULN with accompanying total bilirubin > 2x ULN (biochemical Hy's law). An adequate explanation for the biochemical abnormalities could be identified in all but one case. This one case was classified as a 'probable diagnosis of mild to moderately severe dapagliflozin-induced liver injury'. Imbalances in severe hepatic transaminase elevations (> 5x and 10xULN) between dapagliflozin and comparators were not observed and no signal for hepatotoxicity was identified in the nonclinical program.

Please comment on the clinical relevance of the one case and whether sufficient evaluation has been conducted premarketing to determine if dapagliflozin is associated with a risk of hepatotoxicity.

Breast and Bladder Cancer

3. Numeric imbalances in breast and bladder cancer were observed in the clinical development program. For both of these types of cancer, please discuss whether these imbalances signify a risk of carcinogenic potential associated with dapagliflozin. In addition, please comment on whether the numeric imbalances were impacted by the following:
   a. Any imbalance of baseline risk factors
   b. Any detection bias

Other Safety Findings

4. Please discuss the clinical significance of the following in the T2DM population:
   a. increased genital-urinary infections associated with dapagliflozin therapy
   b. bone safety concerns
   c. any other safety issues identified in the premarketing application

5. Do the efficacy and safety data provide substantial evidence to support approval of dapagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with T2DM? (VOTING)

   a. If yes, do you recommend any further data be obtained post-marketing?
   b. If no, what further data should be obtained?